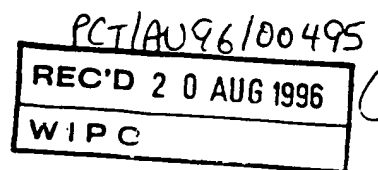




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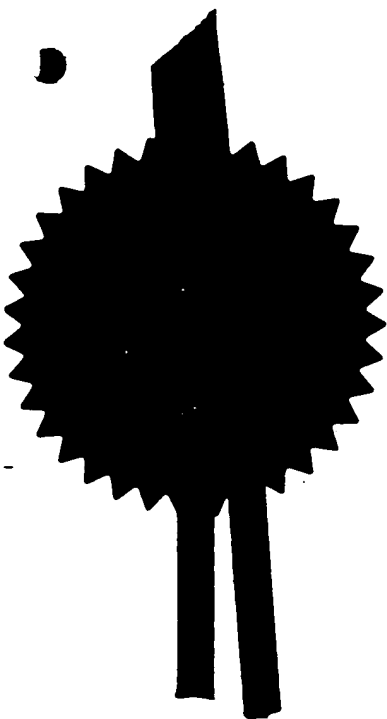
08/735,366

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation and Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated 16.7.96

official use

08 AUG 1995

Your reference
HQ/GR2122

9516276.4

Notes

Please type, or write in dark ink using CAPITAL letters. A prescribed fee is payable for a request for grant of a patent. For details, please contact the Patent Office (telephone 071-438 4700).

Rule 16 of the Patents Rules 1990 is the main rule governing the completion and filing of this form.

2 Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

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After an application for a Patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977 and will inform the applicant if such prohibition or restriction is necessary. Applicants resident in the United Kingdom are also reminded that under Section 23, applications may not be filed abroad without written permission unless an application has been filed not less than 6 weeks previously in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction revoked.

The
Patent
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Request for grant of a Patent Form 1/77

Patents Act 1977

1 Title of invention

CHEMICAL COMPOUNDS

1 Please give the title of the invention

2 Applicant's details

☒ First or only applicant

2a If you are applying as a corporate body please give:

Corporate name

BIOTA SCIENTIFIC MANAGEMENT LTD

Country (and State of incorporation, if appropriate)

AUSTRALIA

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address

P O BOX 1601
GLEN IRIS
VICTORIA 3146

UK postcode
(if applicable)

Country AUSTRALIA

ADP number
(if known)

678260100195

2d, 2e and 2f:
If there are further applicants
please provide details on a separate
sheet of paper.

☒ **Second applicant (if any)**

2d If you are applying as a corporate body please give:

Corporate name

Country (and State of incorporation, if appropriate)

2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2f In all cases, please give the following details:

Address

UK postcode
(if applicable)

Country

ADP number
(if known)

3
An address for service in the United
Kingdom must be supplied.

Please mark correct box

3 Address for service details

3a Have you appointed an agent to deal with your application?

Yes ☒ No ☐ ➡ go to 3b



Please give details below

Agent's name

HELEN KAYE QUILLIN

Agent's address

GLAXO HOUSE

BERKELEY AVENUE

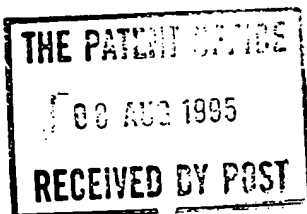
GREENFORD

MIDDLESEX

Postcode UB6 0NN

Agent's ADP
number

06470579001



3b:
If you have appointed an agent,
all correspondence concerning
your application will be sent to
the agent's United Kingdom
address.

3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode
ADP number
(if known)

Daytime telephone
number (if available)

Additional Agents
(See Page 2 No. 3a)

NAME(S)

Alan HESKETH
Laurence David JENKINS
Michael DADSON
Peter I. DOLTON
Hugh B. DAWSON
Wendy Anne. FILLER
Alison GALLAFENT
Michael GARRETT
Catriona McLeod HAMMER
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Michael John STOTT

ADDRESS

Glaxo Wellcome plc
Glaxo House
Berkeley Avenue
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UB6 ONN
Great Britain

4 Agent's or applicant's
reference number
(if applicable) HQ/GR2122

Yes ☐ No ☒ ➡ *go to 6*



please give details below

- **filing date**

(day month year)

- Please mark correct box**

15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

| Country of filing | Priority application number (if known) | Filing date (day, month, year) |
|-------------------|---|-----------------------------------|
| | | |

7

The answer must be 'No' if:

- any applicant is not an inventor
- there is an inventor who is not an applicant, or
- an applicant is a corporate body.

8

Please supply duplicates of claim(s), abstract, description and drawing(s).

Please mark correct box(es)

9

You or your appointed agent (as defined in Rule 90 of the Patents Rules 1990) must sign this request.


Please sign here

A completed fee sheet should preferably accompany the fee.

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark the correct box

Yes ☐ No ☒ 

A statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

Claim(s) Description

Abstract Drawing(s)

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

Patents Form 7/77 - Statement of Inventorship and Right to Grant (please state how many)

Patents Form 9/77 - Preliminary Examination/Search

Patents Form 10/77 - Request for Substantive Examination

9 Request


I/We request the grant of a patent on the basis of this application.

Signed  Date 07/08/1995
(day month year)

H K

Quillin Agent for the Applicants

Please return the completed form, attachments and duplicates where requested, together with the prescribed fee to:

 The Comptroller
The Patent Office
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CHEMICAL COMPOUNDS

This invention relates to a new class of chemical compounds and to their use in medicine. In particular the invention concerns novel dihydropyran derivatives, methods for their preparation, pharmaceutical formulations thereof and their use as antiviral agents.

Enzymes with the ability to cleave N-acetyl neuraminic acid (NANA), also known as sialic acid, from other sugars are present in many microorganisms. These include bacteria such as *Vibrio cholerae*, *Clostridium perfringens*, *Streptococcus pneumoniae*, and *Arthrobacter sialophilus*, and viruses such as influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus, and Sendai virus. Most of these viruses are of the orthomyxovirus or paramyxovirus groups, and carry a neuraminidase activity on the surface of the virus particles.

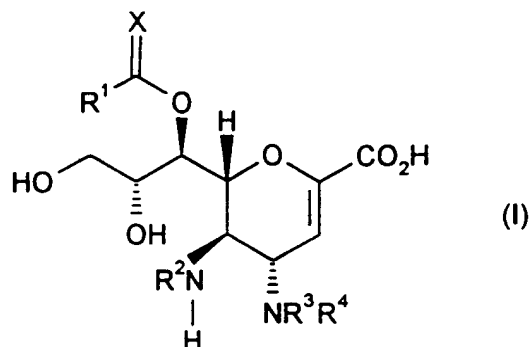
Many of the neuraminidase-possessing organisms are major pathogens of man and/or animals, and some, such as influenza virus and Newcastle disease virus, cause diseases of enormous economic importance.

It has long been thought that inhibitors of neuraminidase activity might prevent infection by neuraminidase-bearing viruses. Most of the known neuraminidase inhibitors are analogues of neuraminic acid, such as 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA) and its derivatives. See, e.g., Meindl et al., *Virology* 1974 58 457-63. International Application Publication No. WO91/16320 describes a number of analogues of DANA active both in vitro and in vivo against viral neuraminidase and useful in the treatment of influenza.

We have now found a novel class of dihydropyran derivatives which are active against the influenza virus.

The invention therefore provides, in a first aspect, compounds of formula (I)

2



wherein

R¹ represents NR⁵R⁶, wherein

R⁵ represents H or a hydrocarbon group optionally substituted by one or more of Br, Cl, F, I, CF₃, NR⁷R⁸, CO₂R⁹, CONR⁷R⁸, COR⁹, OR¹⁰ or SR¹⁰, or a heteroaromatic group; and

R⁶ represents a hydrocarbon group optionally substituted by one or more of Br, Cl, F, I, CF₃, NR⁷R⁸, CO₂R⁹, CONR⁷R⁸, COR⁹, OR¹⁰ or SR¹⁰, or a heteroaromatic group;

R² represents a group SO₂R⁹ or COR⁹;

R³ represents H, C₁₋₆alkyl or C(=NR¹¹)NR¹²R¹³;

R⁴ represents H or C₁₋₆alkyl;

R⁷ and R⁸ each independently represent H, C₁₋₆alkyl or COR⁹;

R⁹ represents C₁₋₆alkyl optionally substituted by one or more halogen atoms;

R¹⁰ represents H, C₁₋₆alkyl or phenyl;

R¹¹, R¹² and R¹³ each independently represent H, C₁₋₆alkyl, amino, hydroxy, cyano or nitro;

X represents O or S;

and their pharmaceutically acceptable derivatives.

In general, it is to be understood that when any variable occurs more than once in formula (I), that variable may be the same on each occasion, or different. In particular, when R⁵ and R⁶ each represent an optionally substituted hydrocarbon group or a heteroaromatic group they may be the same or different.

As used herein, "hydrocarbon group" includes saturated and unsaturated, straight, branched and cyclic hydrocarbon groups, including aryl groups, and combinations of such groups.

Suitable hydrocarbon groups represented by R^6 and/or R^5 include C_{1-20} alkyl, such as propyl, butyl, pentyl, hexyl, heptyl, octanyl, nonyl, decyl, undecyl and dodecyl, C_{5-7} cycloalkyl groups, such as cyclohexyl, phenyl and aralkyl groups such as benzyl. Suitable substituents for the hydrocarbon groups represented by R^6 and/or R^5 include Br, Cl, F, I, CF_3 , NH_2 , substituted amino groups such as $NHCO(C_4H_{10})$, alkoxy groups such as methoxy, and hydroxy.

When R^5 and/or R^6 represents a heteroaromatic group, this will suitably be a pyridyl group optionally substituted by one or more of C_{1-6} alkyl, Br, Cl, F, I and CF_3 .

Preferably R^5 represents H, C_{1-6} alkyl or benzyl.

Preferably R^6 represents optionally substituted C_{1-20} alkyl or benzyl.

More preferably R^5 represents H, C_{1-3} alkyl or benzyl and R^6 represents C_{1-12} alkyl optionally substituted by an unsubstituted or substituted amine, or benzyl.

Preferably R^2 represents COR^9 .

Where R^3 represents $C(=NR^{11})NR^{12}R^{13}$, suitably two of R^{11} , R^{12} and R^{13} represent H and the other of R^{11} , R^{12} and R^{13} is selected from H, C_{1-6} alkyl, such as methyl, NH_2 , OH, CN or NO_2 .

Preferably NR^3R^4 represents amino or guanidino, more preferably guanidino.

Preferably R^9 represents methyl or trifluoromethyl, more preferably methyl.

Preferably X represents O.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of

providing (directly or indirectly) a compound of formula (I) or an antivirally active metabolite or residue thereof.

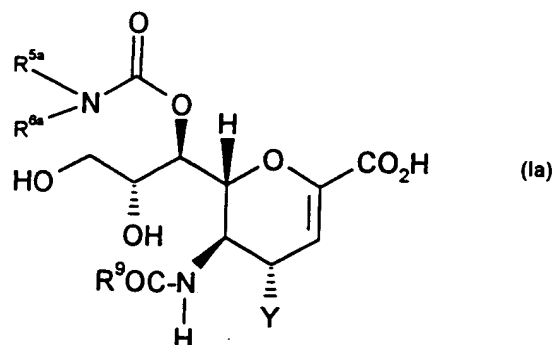
It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds of formula (I). Of particular interest as such derivatives are compounds modified at the carboxyl function, hydroxyl functions or at amino groups. Thus compounds of interest include alkyl (such as methyl, ethyl or propyl e.g. isopropyl) or aryl (e.g. phenyl, benzoyl) esters and acetyl esters of the compounds of formula (I).

It will be appreciated by those skilled in the art that the pharmaceutically acceptable derivatives of the compounds of formula (I) may be derivatised at more than one position.

Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene- p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR_4^+ (where R is C_{1-4} alkyl) salts.

A particular subgroup of compounds according to the invention is represented by formula (Ia):



wherein:

R^9 is as defined for formula (I);

R^{5a} represents H, C_{1-12} alkyl or benzyl;

R^{6a} represents optionally substituted C_{1-12} alkyl or benzyl;

Y represents an amino or guanidino group;

and pharmaceutically acceptable salts or esters thereof.

When R^{6a} represents optionally substituted C_{1-12} alkyl, suitable substituents include substituted and unsubstituted amines.

Particular compounds according to the invention include:

(4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoxyloxy-2R,3-dihydroxy-propyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid;

(4S,5R,6R)-5-Acetylamino-6-(1R-dodecylcarbamoxyloxy-2R,3-dihydroxy-propyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid;

(4S,5R,6R)-5-Acetylamino-6-{1R-[(6-amino-hexyl)carbamoxyloxy]-2R,3-dihydroxypropyl}-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid;

and pharmaceutically acceptable derivatives thereof.

References hereinafter to a compound of the invention include the compounds of formula (I) and pharmaceutically acceptable derivatives thereof.

The compounds of formula (I) possess antiviral activity. In particular these compounds are inhibitors of viral neuraminidase of orthomyxoviruses and paramyxoviruses in particular neuraminidase, for example the viral

neuraminidase of influenza A and B, parainfluenza, mumps and Newcastle disease.

There is thus provided in a further aspect of the invention a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use as an active therapeutic agent in particular as an antiviral agent for example in the treatment of orthomyxovirus and paramyxovirus infections.

In a further or alternative aspect there is provided a method for the treatment of a viral infection, for example orthomyxovirus and paramyxovirus infections in a mammal including man comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof.

In a preferred aspect there is provided a method for the treatment of influenza A or B in a mammal including man comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof.

There is also provided in a further or alternative aspect use of a compound of the invention for the manufacture of a medicament for the treatment of a viral infection.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

The compounds of the invention may also be used in diagnostic methods, in particular methods for the detection of influenza virus. For use in such methods it may be advantageous to link a compound of the invention to a label.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at

the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.1 to 750mg/kg of bodyweight per day, preferably in the range of 0.5 to 60 mg/kg/day, most preferably in the range of 1 to 20mg/kg/day.

Treatment is preferably commenced before or at the time of infection and continued until virus is no longer present in the respiratory tract. However the compounds are also effective when given post-infection, for example after the appearance of established symptoms.

Suitably treatment is given 1-4 times daily and continued for 3-7, e.g. 5 days post infection depending upon the particular compound used.

The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form for example containing 10 to 1500mg, conveniently 20 to 1000mg, most conveniently 50 to 700mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (1) or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form

suitable for administration to the respiratory tract (including the nasal passages) for example by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with

an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For administration to the respiratory tract (including intranasal administration) according to the method of the invention the neuraminidase inhibitors may be administered by any of the methods and formulations employed in the art for administration to the respiratory tract.

Thus in general the compounds may be administered in the form of a solution or a suspension or as a dry powder.

Solutions and suspensions will generally be aqueous for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, polyethylene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients for example preservatives (such as benzalkonium chloride), solubilising agents/surfactants such as polysorbates (e.g. Tween 80, Span 80, benzalkonium chloride), buffering agents, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the compounds may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g. gelatin or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size

for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The compounds of the invention may also be used in combination with other therapeutic agents, for example other anti-infective agents. In particular the compounds of the invention may be employed with other antiviral agents. The invention thus provides in a further aspect a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof together with another therapeutically active agent, in particular an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus such formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

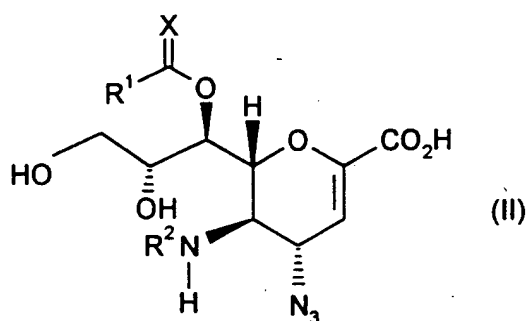
Suitable therapeutic agents for use in such combinations include other anti-infective agents, in particular anti-bacterial and anti-viral agents such as those used to treat respiratory infections. For example, other compounds effective against influenza viruses, such as amantadine, rimantadine and ribavirin, may be included in such combinations.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compounds of the invention are used with a second therapeutic agent active against the same virus the dose of each compound may either be the same as or differ from that employed when each compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compounds of formula (I) and their pharmaceutically acceptable salts and derivatives may be prepared by the methods described below in which R^1 , R^2 , R^3 , R^4 and X are as defined for formula (I) unless otherwise specified. The methods outlined below form a further aspect of the invention.

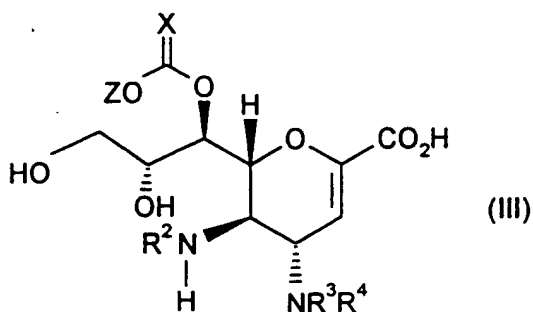
In one such process (A) compounds of formula (I) wherein R^3 and R^4 each represent H may be prepared from compounds of formula (II)



or a suitably protected derivative thereof, by reduction of the azide group, followed, if necessary, by deprotection.

The reduction may be carried out using any known methods for the conversion of azides to amines. Suitable methods are described in the Examples hereinafter and, for example, in International patent applications publication numbers 93/12105 and 95/00503.

According to a second process, (B), compounds of formula (I) may be prepared from intermediates of formula (III):

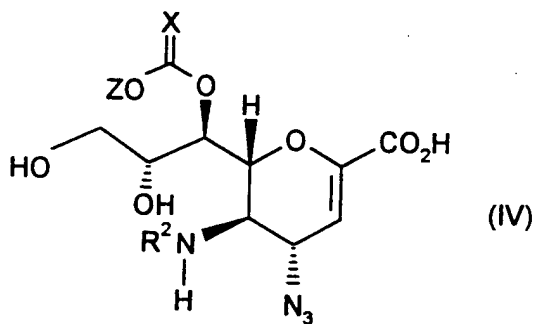


or protected derivatives thereof wherein Z represents an activating group, for example para-nitrophenyl, by reaction with a compound of formula HNR^5R^6 in the presence of a base, such as an organic base, for example, pyridine and, preferably, a suitable catalyst, such as dimethylaminopyridine (DMAP).

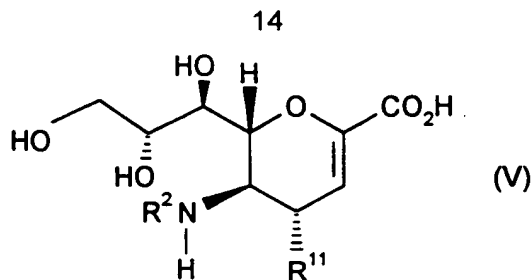
Compounds of formula (I) may also be prepared from other compounds of formula (I) by interconversion reactions. For example, compounds wherein R^3 and R^4 are other than H may be prepared by derivatisation of the corresponding compound wherein R^3 and/or R^4 are H. In particular, compounds of formula (I) wherein R^3 represents $\text{C}(=\text{NR}^{11})\text{NR}^{12}\text{R}^{13}$ may be prepared from corresponding compounds of formula (III) wherein R^3 is H, for example, by reaction with pyrazolcarboxamidine, or a derivative thereof.

Similarly, compounds of formula (I) may be converted to their pharmaceutically acceptable derivatives, e.g. salts or esters, by conventional techniques.

Compounds of formula (II) may be prepared from the corresponding compounds of formula (IV):



or protected derivatives thereof, wherein Z is as previously defined, analogously to the preparation of compounds of formula (I) from compounds of formula (III). Intermediates of formula (III) and (IV) may be prepared from the corresponding compounds of formula (V):



or protected derivatives thereof, wherein R¹¹ represents NR³R⁴ as previously defined or N₃, by reaction with a compound of formula ZOC(=X)Cl in the presence of a base, such as an organic base, for example, pyridine and, preferably, a suitable catalyst such as, for example, DMAP.

Compounds of formula (V) are known compounds. Their preparation is described, for example, in International Patent Application publication No. 91/16320.

Intermediates of formulae (II), (III) and (IV) are novel compounds and comprise a further aspect of the present invention.

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the above described processes to protect one or more sensitive groups in the molecule to prevent undesirable side reactions; the protecting group may be removed at any convenient subsequent stage in the reaction sequence.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed. J. F. W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene and P G M Wuts (John Wiley and Sons 1991).

Conventional amino protecting groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl.

Hydroxy or carboxy groups may be protected, for example, by aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups, acyl groups, such as acetyl, acetal, silicon protecting groups, such as trimethylsilyl groups, or as tetrahydropyran derivatives.

Removal of any protecting groups present may be achieved by conventional procedures.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I) with an appropriate acid, preferably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. aqueous ethanol).

The present invention is further described by the following examples which are for illustrative purposes only and should not be construed as a limitation of the invention.

Example 1

(4S,5R,6R)-5-Acetylamino-4-amino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxy-propyl)-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (1): (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-hydroxy-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

To a suspension of (4S,5R,6R)-5-Acetylamino-4-azido-6-(1R,2R,3-trihydroxy-propyl)-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester (8.2g) in dry acetonitrile (100ml) and dry dichloromethane (200ml) was added 4-dimethylaminopyridine (8.6g). A 20% solution of phosgene in toluene (18ml) was added slowly dropwise and the reaction mixture was stirred at room temperature for 2 hours. The solution was then added to ice cold 1M potassium dihydrogen orthophosphate solution (400ml) and extracted with ethyl acetate (350mlx3). The combined organic extracts were washed with saturated aqueous NaCl (30ml), dried (Na₂SO₄), and the solvent removed under vacuum to yield an orange foam which was purified by flash chromatography on a silica

column (Merck 9385, chloroform/methanol 15:1) to give the title compound (6.008g) as an off-white foam.

TLC silica (chloroform/methanol 15:1) R_f 0.13

m/z MNH_4^+ = 374

Intermediate (2): (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-heptylcarbamoyloxy-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

To an ice-cold solution of Intermediate 1 (1g) in dry dichloromethane (10ml) was added 4-dimethylaminopyridine (349mg) and n-heptyl isocyanate (1g). The solution was warmed to room temperature and stirred for 21 hours under nitrogen. The reaction was then quenched by the addition of methanol (1ml) and the solution stirred for 15 min then added to ice cold 1M potassium dihydrogen orthophosphate solution (100ml) and extracted with ethyl acetate (175mlx3). The combined organic extracts were washed with concentrated aqueous NaCl (30ml), dried (Na_2SO_4) and the solvent removed under vacuum to yield an orange solid which was purified by flash chromatography on a silica column (Merck 9385, chloroform/methanol 20:1) to give the title compound (560mg) as a white foam.

TLC silica (chloroform/methanol 9:1) R_f 0.34

m/z MH^+ = 498

(4S,5R,6R)-5-Acetylamino-4-amino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxy-propyl)-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

A mixture of Intermediate 2 (383mg) and triphenylphosphine (253mg) in dry tetrahydrofuran (10ml) was stirred under nitrogen for 20 hours. To this was added triethylamine (5ml) and water (13ml) and the solution was heated at 40⁰ for a further 24 hours. The reaction mixture was washed with ethyl acetate (20ml), the organic phase re-extracted with water (5ml) and the combined aqueous phases evaporated under vacuum. The residue was purified by preparative Hplc (Microsorb C18) using a water/acetonitrile/trifluoroacetic acid elution gradient. The freeze-dried solid obtained was taken up in methanol (2 drops) and precipitated using diethyl ether (10ml) to give the title compound (215mg) as a white powder.

m/z MH^+ = 432.3

Analysis Found : C, 45.8; H, 6.5; N, 7.75.

$C_{19}H_{33}N_3O_8.CF_3CO_2H$ requires C, 46.2; H, 6.3; N, 7.7

Example 2

(4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxypropyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (3): (4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxypropyl)-4-[2,3-bis(tert-butoxycarbonyl)-guanidino]-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

A solution of the compound of Example 1 (190mg), triethylamine (0.1ml) and N,N'-bis-t-butoxycarbonyl-1H-pyrazole-1-carboxamidine (179mg) in dry methanol (3ml) was stirred under nitrogen for 48 hours and then evaporated under vacuum. The residue obtained was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/glacial acetic acid 95:5) to give the title compound (218mg) as a white solid.

NMR(d_6 -DMSO) δ 8.17 (1H, d), 7.90 (1H, d), 7.13 (1H, t), 5.67 (1H, s), 4.80 (1H, d), 4.68 (1H, t), 4.39 (1H, d), 3.99 (1H, m), 3.83 (1H, m), 3.40 (1H), 3.24 (1H), 2.88 (2H, m), 1.92 (3H, s), 1.44 (9H, s), 1.40 (9H, s), 1.23 (10H, m), 0.86 (3H, t).
m/z MH^+ =674.4

(4S,5R,6R)-5-Acetylamino-6-(1R-heptylcarbamoyloxy-2R,3-dihydroxypropyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

A solution of Intermediate 3 (104mg) in dry dichloromethane (1ml) and trifluoroacetic acid (1ml) was stirred under nitrogen for 2 hours and then evaporated under vacuum. The residue was taken up in methanol (2 drops) and precipitated using diethyl ether (5ml) to yield a white solid which was purified by preparative Hplc (Microsorb C18) using a water/acetonitrile/trifluoroacetic acid elution gradient. The freeze-dried solid obtained was taken up in methanol (2 drops) and precipitated using diethyl ether (5ml) to give the title compound (29mg) as a white powder.

NMR(d_6 -DMSO) δ 7.98 (1H, br d), 7.57 (1H, br d), 7.40 (3H, br s), 7.17 (1H, br t), 5.54 (1H, br d), 4.82 (1H, d), 4.2-4.38 (2H, 2xdd), 3.96 (1H, q), 3.82 (1H, td), ~3.3 (2H, m), 2.88 (2H, q), 1.77 (3H, s), 1.12-1.49 (10H, m), 0.87 (3H, t).
m/z MH^+ =474. MS calcd. for $C_{20}H_{36}N_5O_8$ (MH^+): 474.2564. Found 474.2562

Analysis Found: C, 44.1; H, 6.6; N, 11.9.

$C_{20}H_{35}N_5O_8 \cdot CF_3CO_2H \cdot 0.5H_2O$ requires C, 44.3; H, 6.25; N, 11.7

Example 3

(4S,5R,6R)-5-Acetylamino-6-(1R-dodecylcarbamoyloxy-2R,3-dihydroxypropyl)-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (4): (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-hydroxy-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

A suspension of (4S,5R,6R)-5-Acetylamino-4-azido-6-(1R,2R,3-trihydroxypropyl)-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester (10g) was stirred in acetaldehyde diethyl acetal (250ml) for one hour; this solution was stirred for a further 30 minutes after the addition of p-toluenesulphonic acid (30mg) and then left to stand for 16 hours. The crystalline solid was filtered and dried to give the title compound (5g) as a pale orange solid.

TLC silica (chloroform/methanol 9:1) R_f 0.30

m/z $MNH_4^+ = 526$

Intermediate (5): (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-dodecylcarbamoyloxy-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

To an ice-cold suspension of Intermediate 4 (2.96g) in dry dichloromethane (115ml) and dry acetonitrile (125ml) was added 4-dimethylaminopyridine (877mg) and n-dodecyl isocyanate (7.5ml). The reaction mixture was heated at 45° under nitrogen for 89 hours. The reaction was quenched by the addition of methanol (6ml), and concentrated to ~80ml then added to 1M potassium dihydrogen orthophosphate solution (250ml) and extracted with ethyl acetate (300mlx2). The combined organic extracts were washed with concentrated aqueous NaCl (60ml), dried (Na_2SO_4) and the solvent removed under vacuum to yield a yellow foam which was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/petroleum ether (40-60) 1:1) to give the title compound (1.247g) as a yellow foam.

TLC silica (ethyl acetate/petroleum ether (40-60) 1:1) R_f 0.31

m/z $MH^+ = 720.2$, $MNa^+ = 742.2$

Intermediate (6): (4S,5R,6R)-5-Acetylamino-4-amino-6-[(S)-dodecylcarbamoyloxy-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

A mixture of Intermediate 5 (1.139g) and triphenylphosphine (517mg) in dry tetrahydrofuran (20ml) was heated at 40⁰ under nitrogen for 24 hours. To this was added triethylamine (11ml) and water (17ml) and the reaction mixture was heated at 40⁰ for 2 hours and then evaporated to yield a yellow solid which was purified by flash chromatography on a silica column (Merck 9385, chloroform/methanol 15:1) to give the title compound (761mg) as a yellow foam. TLC silica (chloroform/methanol 15:1) R_f 0.14

m/z MS calcd. for C₃₉H₅₆N₃O₈ (MH⁺):694.4067. Found 694.4062

Intermediate (7): (4S,5R,6R)-5-Acetylamino -6-[(S)-dodecylcarbamoyloxy-(2-oxo-[1,3]-dioxolan-4R-yl)-methyl]-4-[2,3-bis(tert-butoxycarbonyl)-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

A suspension of Intermediate 6 (670mg) and bis (t-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (390mg) in dry tetrahydrofuran (8ml) was stirred under nitrogen at 35⁰ for 48 hours and then evaporated under vacuum to yield an off-white foam which was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/petroleum ether (40-60) 1:2) to give the title compound (815mg) as a white solid.

TLC silica (ethyl acetate/petroleum ether (40-60) 1:2) R_f 0.13

m/z MH⁺=936.6

(4S,5R,6R)-5-Acetylamino -6-(1R-dodecylcarbamoyloxy-2R,3-dihydroxypropyl)-4-guanidino -5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

A solution of Intermediate 7 (637mg) in glacial acetic acid/water 4:1 (20ml) was heated at 85⁰ for 2 hours and then evaporated under vacuum to yield a white solid which was stirred in dry dichloromethane (6ml) and trifluoroacetic acid (5ml) for 26 hours. The solvent was removed under vacuum to yield a green foam which was purified by reverse phase silica column chromatography (Merck, LiChroprep RP-18, water/acetonitrile/trifluoroacetic acid 50:50:1) to give the title compound (209mg) as a freeze-dried white powder.

NMR(d_6 -DMSO) δ 7.98 (1H, br d), 7.57 (1H, br d), 7.36 (3H, br s), 7.18 (1H, br t), 5.57 (1H, br d), 4.83 (1H, dd), 4.33 (1H, dd), 4.25 (1H, dd), 3.97 (1H, q), 3.82 (1H, td), ~3.4 (2H, m), 2.88 (2H, q), 1.78 (3H, s), 1.1-1.47 (20H, m), 0.86 (3H, t).
 m/z MH^+ =544.3

Analysis Found: C, 49.3; H, 7.4; N, 10.8.

$C_{25}H_{45}N_5O_8 \cdot CF_3CO_2H$ requires C, 49.3; H, 7.05; N, 10.65

Example 4

(4S,5R,6R)-5-Acetylamino-4-amino-6-{2R,3-dihydroxy-1R-[(6-tert-butoxycarbonylamino)hexyl]-carbamoyloxy]-propyl}-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (8): (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-(4-nitro-phenoxy)carbonyloxy]-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

To a solution of (4S,5R,6R)-5-Acetylamino-4-azido-6-(1R,2R,3-trihydroxy-propyl)-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester (3.3g) in dry pyridine (30ml), under nitrogen, was added 4-nitrophenylchloroformate (2.42g). After stirring at room temperature for 2.5 hours a further portion of 4-nitrophenylchloroformate (2g) was added followed by 4-dimethylaminopyridine (3.05g). Stirring was continued at room temperature for 3.5 hours. The solution was concentrated under vacuum and the residue was partitioned between 2M HCl (200ml) and ethyl acetate (100ml). The layers were separated and the aqueous phase was further extracted with ethyl acetate (100ml x2). The combined organic extracts were washed with saturated aqueous NaCl (60ml), dried (Na_2SO_4) and the solvent removed under vacuum to yield a beige foam which was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/cyclohexane 2:1) to give the title compound (3.21g) as a white foam.

NMR(d_6 -DMSO) δ 8.36 (2H, d), 8.22 (1H, d), 7.61 (2H, d), 5.94 (1H, d), 5.50 (1H, t), 5.35 (1H, m), 4.72 (1H, t), 4.60 (1H, t), 4.40-4.50 (2H, m), 4.23 (1H, t), 3.78 (3H, s), 1.86 (3H, s).

TLC silica (ethyl acetate/cyclohexane 2:1) R_f 0.16

m/z MH^+ =522

Intermediate (9): (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-[(2-oxo-[1,3]dioxolan-4R-yl)-(6-tert-butoxycarbonylaminohexyl)-carbamoyloxy]-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid methyl ester

To a solution of Intermediate 8 (1.15 g) in dry pyridine was added 4-dimethylaminopyridine (648 mg) and N-Boc-1,6-diaminohexane hydrochloride (670 mg). The solution was stirred at room temperature for 18 hours. 2M aqueous hydrochloric acid (150 ml) was added to the solution and extracted with ethyl acetate (50 ml x 2). The combined organic extracts were washed with saturated aqueous NaCl (10 ml), dried (Na₂SO₄) and the solvent removed under vacuum to yield a yellow foam which was purified by flash chromatography on a silica column (Merck 9385, ethyl acetate/ cyclohexane 4:1) to give the title compound (1.155 g) as a pale yellow foam.

NMR (CDCl₃) δ 6.31 (1H, br.d), 5.95 (3H, d), 5.42 (1H, dd), 4.5-5.2 (7H, m), 3.80 (3H, s), 3.0-3.4 (5H, m), 2.06 (3H, s), 1.50 (4H, m), 1.44 (9H, s), 1.34 (4H, m).

TLC silica (ethyl acetate/cyclohexane 4:1) R_f 0.28

Analysis Found: C, 49.6; H, 6.4; N, 13.4

C₂₅H₃₈N₆O₁₁·0.35C₄H₈O₂ requires C, 49.6; H, 6.45; N, 13.9

(4S,5R,6R)-5-Acetylamino-4-amino-6-[2R,3-dihydroxy-1R-[(6-tert-butoxycarbonylaminohexyl)-carbamoyloxy]-propyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

To a solution of Intermediate 9 (1.05 g) in dry tetrahydrofuran (40 ml) was added triphenylphosphine (610 mg) and the solution was stirred at room temperature for 18 hours. To this was added triethylamine (12 ml) and water (31 ml) and the solution was heated at 40° for a further 28 hours. The reaction mixture was evaporated to yield a yellow gum which was purified by flash reverse-phase chromatography (Merck 13900, water (containing trifluoroacetic acid 0.1%)/acetonitrile 8:2). The gum obtained by freeze-drying was triturated vigorously for one hour at room temperature to give the title compound as a buff powder.

NMR(d₆-DMSO) δ 7.92 (1H, d), 7.13 (1H, t), 6.75 (1H, t), 5.70 (1H, s), 4.85 (1H, d), 4.34 (1H, d), 4.02 (1H, q), 3.85 (1H, t), 3.77 (1H, d), 3.25, 3.44 (2H, m), 2.90 (4H, m), 1.82 (3H, s), 1.18-1.42 (8H, m), 1.38 (9H, s).

m/z MH⁺=533

Analysis Found: C, 47.65; H, 6.75; N, 8.8

C₂₃H₄₀N₄O₁₀.CF₃CO₂H.0.25C₆H₁₅N requires C, 47.4; H, 6.7; N, 8.9

Example 5

(4S,5R,6R)-5-Acetylamino-6-{1R-[(6-aminohexyl)carbamoyl-oxy]-2R,3-dihydroxy-propyl}-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (10): (4S,5R,6R)-5-Acetylamino -6-{1R-[(6-tert-butoxy-carbonylamino)hexyl)carbamoyloxy]-2,3-dihydroxypropyl}-4-[2,3-bis(tert-butoxycarbonyl)guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid

A solution of the compound of Example 4 (0.75 g), triethylamine (0.5 ml) and N,N'-bis-(t-butoxycarbonyl)-1H-pyrazole-1-carboxamide (0.54 g) in a mixture of dry tetrahydrofuran (10 ml) and dry methanol (3 ml) was stirred under nitrogen for 20 hours and then evaporated under vacuum. The residue was dissolved in ethyl acetate (100 ml), stirred vigorously with water (20 ml) and the pH of the mixture was adjusted to pH 2 with 2M hydrochloric acid. The organic layer was washed with saturated aqueous NaCl (20 ml), dried (Na₂SO₄), and the solvent removed under vacuum to yield a yellow foam which was purified by flash chromatography on a silica column (Merck 9385, chloroform/methanol 7:1) to give the title compound (0.37 g) as a white solid.

NMR (d₆-DMSO) δ 11.42 (1H, s), 8.25 (1H, d), 7.95 (1H, d), 7.16 (1H, t), 6.75 (1H, t), 5.80 (1H, s), 4.82 (1H, d), 4.74 (1H, t), 4.43 (1H, d), 4.0 (4H, m), 3.25 (1H, m), 2.90 (4H, m), 1.76 (3H, s), 1.49 (9H, s), 1.38 (18H, s), 1.2-1.5 (8H, m).

TLC silica (chloroform/methanol 3:1) R_f 0.21

m/z MH⁺=775

(4S,5R,6R)-5-Acetylamino-6-{1R-[(6-aminohexyl)carbamoyloxy]-2R,3-dihydroxy-propyl}-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

A solution of Intermediate 10 (325 mg) in trifluoroacetic acid (10 ml) was stirred under nitrogen for 1 hour and evaporated under vacuum. The residue was dissolved in water (10 ml), stirred for one hour and the water removed by lyophilisation to give the title compound (255 mg) as a white solid.

NMR (d₆-DMSO) δ 7.97 (1H, d), 7.69 (2H, br.s), 7.6 (1H, d), 7.2 (3H, m), 5.72 (1H, s), 5.07 (1H, d), 4.85 (1H, d), 4.4 (2H, m), 4.33 (1H, t), 4.02 (1H, q), 3.83

(1H, m), 3.3 (1H, m), 3.4 (1H, m), 2.91 (2H, m), 2.78 (2H, m), 1.81 (3H, s), 1.2-1.6 (8H, m)

m/z MH⁺=475

TLC silica (butanol/acetic acid/water 3:1:1) R_f 0.17

Example 6

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-dicyclohexylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Intermediate (11) (4S,5R,6R)-5-Acetylamino-4-azido-6-[(S)-(1,1-dicyclohexylcarbamoyloxy)-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

A mixture of Intermediate 4 (1 g) in dry pyridine, and dicyclohexylcarbamoyl chloride (1.46 g) was heated under nitrogen at 100 °C for six hours. The mixture was concentrated under vacuum and the residue treated with 30 % citric acid. The aqueous mixture was extracted with ethyl acetate (50ml x 2). The combined organic extracts were washed with 10 % sodium hydrogen carbonate solution (20ml), saturated aqueous NaCl (20ml), dried (Na₂SO₄) and the solvent removed under vacuum to yield an orange foam which was purified by flash chromatography on a silica column (Merck 9385, chloroform : methanol 20 : 1) to give the title compound (0.69g) as a colourless foam.

TLC silica (diethyl ether/pet.ether (40:60) 3:1) R_f 0.14

Analysis Found: C, 65.6; H, 6.6; N, 9.4.

C₃₉H₄₉N₅O₈ requires C, 65.4; H, 6.9; N, 9.8

Intermediate (12) (4S,5R,6R)-5-Acetylamino-4-amino-6-[(S)-(1,1-dicyclohexylcarbamoyloxy)-(2-oxo-[1,3]dioxolan-4R-yl)-methyl]-5,6-dihydro-4H-pyran-2-carboxylic acid benzhydryl ester

The title compound was prepared from Intermediate 11 analogously to the preparation of Intermediate 6 from Intermediate 5.

NMR (CDCl₃) δ 7.3 (10H, m), 6.94 (1H, s), 6.1 (2H, m), 5.25 (1H, dd), 4.95 (1H, q), 4.6 (1H, dd), 4.4-4.1 (3H, m), 3.9 (1H, m), 3.6 (1H, m), 3.2 (2H, m), 2.05 (3H, s), 1.3 (3H, d), 1.8-1.0 (20H, m)

Analysis Found: C, 64.2; H, 6.9; N, 5.65

C₃₉H₅₁N₃O₈.0.4CHCl₃ requires C, 64.2; H, 7.0; N, 5.7

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-dicyclohexylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

The title compound was prepared from Intermediate 12 analogously to the preparation of Example 3 from Intermediate 7.

MS calc. for $C_{24}H_{40}N_3O_8$ MH^+ : 498.281541

Found: 498.280751

Analysis Found: C, 45.0; H, 6.2; N, 5.6

$C_{24}H_{39}N_3O_8 \cdot 2(CF_3CO_2H) \cdot H_2O$ requires: C, 45.2; H, 5.8; N, 5.65

Example 7

(4S,5R,6R)-5-Acetylamino-6-[1R-(1,1-dicyclohexylcarbamoyloxy)-2R,3-dihydroxypropyl]-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 3.

Analysis Found: C, 45.5; H, 6.0; N, 9.5

$C_{25}H_{41}N_5O_8 \cdot 2(CF_3CO_2H)$ requires: C, 45.4; H, 5.65; N, 9.1

TLC R_f = 0.65, n-butanol : acetic acid : water, 3 : 1 : 1

Example 8

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-benzylcarbamoyloxy-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 1.

MS calc. for $C_{19}H_{26}N_3O_8$ MH^+ : 424.171990

Found: 424.171552

TLC R_f = 0.40, n-butanol : acetic acid : water, 3 : 1 : 1

Example 9

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-n-propylcarbamoyloxy-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 1.

MS calc. for $C_{15}H_{26}N_3O_8$ MH^+ : 376.171990

Found: 376.1732

TLC R_f = 0.31, n-butanol : acetic acid : water, 3 : 1 : 1

Example 10

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-n-dodecylcarbamoyloxy-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 1.

MS calc. for $C_{24}H_{44}N_3O_8$ MH^+ : 502.312841

Found: 502.314514

Analysis Found: C, 50.5; H, 7.35; N, 6.8

$C_{24}H_{43}N_3O_8 \cdot CF_3CO_2H$ requires: C, 50.7; H, 7.2; N, 6.8

Example 11

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-diisopropylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 6.

Analysis Found: C, 41.0; H, 5.5; N, 6.6

$C_{18}H_{31}N_3O_8 \cdot 1.6 CF_3CO_2H \cdot H_2O$ requires: C, 41.2; H, 5.6; N, 6.8

TLC R_f = 0.41, n-butanol : acetic acid : water, 3 : 1 : 1

Example 12

(4S,5R,6R)-5-Acetylamino-6-[1R-(1,1-diisopropylcarbamoyloxy)-2R,3-dihydroxypropyl]-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 3.

MS calc. for $C_{19}H_{34}N_5O_8$ MH^+ : 460.240739

Found: 460.241167

Analysis Found: C, 42.8; H, 6.4; N, 11.45

$C_{19}H_{33}N_5O_8 \cdot CF_3CO_2H \cdot H_2O$ requires: C, 42.6; H, 6.1; N, 11.8

Example 13

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-dibenzylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 4.

MS calc. for $C_{25}H_{32}N_3O_8$ MH^+ : 514.218940

Found: 514.218791

TLC R_f = 0.51, n-butanol : acetic acid : water, 3 : 1 : 1

Example 14

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-di-n-propylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 4.

MS calc. for $C_{18}H_{32}N_3O_8$ MH^+ : 418.218940

Found: 418.219123

Analysis Found: C, 41.7; H, 5.7; N, 6.8

$C_{18}H_{31}N_3O_8 \cdot 1.5 CF_3CO_2H \cdot H_2O$ requires: C, 41.6; H, 5.7; N, 6.9

Example 15

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-cyclohexylcarbamoyloxy-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 6.

Analysis Found: C, 42.6; H, 5.7; N, 7.2

$C_{24}H_{29}N_3O_8 \cdot CF_3CO_2H \cdot 2H_2O$ requires: C, 42.5; H, 6.1; N, 7.4

TLC R_f = 0.44 n-butanol : acetic acid : water, 3 : 1 : 1

Example 16

(4S,5R,6R)-5-Acetylamino-6-[1R-(1,1-dihexylcarbamoyloxy)-2R,3-dihydroxypropyl]-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 5.

Analysis Found: C, 46.3; H, 6.8; N, 9.6

$C_{25}H_{45}N_5O_8 \cdot 1.3 CF_3CO_2H \cdot 1.3H_2O$ requires: C, 46.3; H, 6.9; N, 9.8

TLC R_f = 0.59, n-butanol : acetic acid : water, 3 : 1 : 1

Example 17

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-(1,1-n-heptylbenzylcarbamoyloxy)-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 4.

Analysis Found: C, 48.7; H, 6.0; N, 5.85

$C_{26}H_{39}N_3O_8 \cdot 1.5 CF_3CO_2H \cdot 1.5H_2O$ requires: C, 48.4; H, 6.1; N, 5.8

TLC R_f = 0.53, n-butanol : acetic acid : water, 3 : 1 : 1

Example 18

(4S,5R,6R)-5-Acetylamino-6-[1R-(1,1-n-heptylbenzylcarbamoyloxy)-2R,3-dihydroxypropyl]-4-guanidino-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 5.

Analysis Found: C, 48.3; H, 5.8; N, 9.6

C₂₇H₄₁N₅O₈.1.5 CF₃CO₂H.0.5H₂O requires: C, 48.45; H, 5.9; N, 9.4

TLC R_f = 0.58, n-butanol : acetic acid : water, 3 : 1 : 1

Example 19

(4S,5R,6R)-5-Acetylamino-4-amino-6-[1R-[(6-aminohexyl)carbamoyloxy]-2R,3-dihydroxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid trifluoroacetate

Prepared analogously to Example 5.

MS calc. for C₁₈H₃₃N₄O₈ MH⁺: 433.229839

Found: 433.231597

TLC R_f = 0.12, n-butanol : acetic acid : water, 3 : 1 : 1

Example 20

Inhibition of Influenza Virus

The ability of compounds of the invention to inhibit the multiplication of influenza virus was determined using the method described in WO91/16320. The compounds of the Examples showed activity against influenza A and influenza B virus in this plaque reduction assay. For example, compounds of Examples 1 to 5 had I₅₀ values for influenza A and influenza B of less than 7 µg/ml.